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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/923,132	08/06/2001	Gary S. Sayler	6704-15-1	8944

43463 7590 06/07/2005

RUDEN, MCCLOSKY, SMITH, SCHUSTER & RUSSELL, P.A.
222 LAKEVIEW AVE
SUITE 800
WEST PALM BEACH, FL 33401-6112

EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/923,132	SAYLER ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,8-12,16,18,19,23,25 and 29-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,8-12,16,18,19,23,25 and 29-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed March 7, 2005.

Claims 1-3, 5, 8-12, 16, 18, 19, 23, 25, 27 and 29-48 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed November 5, 2004, that is not addressed in this action has been withdrawn.

Information Disclosure Statement

The information disclosure statement filed March 7, 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

MAINTAINED REJECTIONS

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention. **This rejection is maintained for the reasons set forth in the previous Office Action**.

Claims 29-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a device enclosed in a water-tight packaging, wherein the device comprises an encapsulated bacteria capable of producing a detectable signal in response to mercury, does not reasonably provide enablement for a device enclosed in a water-tight packaging, wherein the device comprises an encapsulated bacteria capable of producing a detectable signal in response to any analyte. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This rejection is maintained for the reasons set forth in the previous Office Action**.

Response to Arguments Concerning Claim Rejections - 35 USC § 112

Applicant's arguments filed March 7, 2005 have been fully considered but they are not persuasive. Applicant provides the following grounds of traversal concerning the rejections under 35 USC § 112, first paragraph (both Written Description and Enablement rejections will be considered simultaneously):

1. Applicant asserts that the previous Office Action indicates "the specification is enabling for a device in a water-tight packaging" (original emphasis)(see for example the last three lines of page 12 in Applicant's Remarks).

2. Applicant argues that numerous cells capable of producing a signal in response to an analyte were known prior to the filing date of the present application, and cites three specific examples

(see for example the bridging paragraph of pages 13-14 in Applicant's Remarks). Applicant then states that, "perhaps, cells do not exist to detect every possible analyte in a universe of different analytes" (see specifically page 14, lines 9 and 10 of Applicant's remarks).

3. Applicant asserts that "[a] patent need not teach, and preferably omits, what is well known in the art" (original emphasis) (see for example the bottom paragraph of page 14 in Applicant's Remarks). Applicant further states that the description need only describe in detail that which is new or not conventional (see for example the second paragraph on page 16 of Applicant's Remarks).

4. Applicant argues that "a 'representative number of species' means that the species which are adequately described are representative of the entire genus...[and] one species [can] adequately support a genus" (see for example the first full paragraph of page 18 of Applicant's response). Applicant then opines that "one of [ordinary] skill in the art would not have to perform undue experimentation to make and use the invention as claimed," (original emphasis), pointing to the "extensive yet not comprehensive list in Appendix A" to support this statement (see for example the first full paragraph of page 15 and the bridging paragraph of pages 16-17 in Applicant's Remarks), and by suggesting that the mercury response element described in the specification is an adequate representation of ALL analyte response elements (see for example the bridging paragraph of page 18-19 in Applicant's Remarks).

5. Applicant argues that the presence of only a single working example cannot support a rejection under 35 USC § 112, first paragraph because "one must evaluate all the facts and evidence and state why one would not expect to extrapolate that one example across the entire scope of the claims;" Applicant then opines that the single example of the mercury detection

system would allow this extrapolation (see for example the bottom paragraph of page 15 of Applicant's Remarks).

Applicant's arguments are not considered persuasive for the following reasons:

1. The previous Office Action *never* states that the specification is enabling for a device in a water-tight packaging; rather, it states it is enabling for a device in a water-tight packaging wherein the device comprises an encapsulated bacteria capable of producing a detectable signal in response to mercury (emphasis added; see for example page 5, lines 17-21 of the previous Office Action). This is the basis for the rejection.

2. Applicant is claiming a device that can produce a detectable signal in response to *any* analyte. By definition, an analyte is *any* composition that can be analyzed; i.e., *any* composition. While there are a few known promoter response elements for the detection of a small number of analytes (Applicant presents a short list of promoter elements capable of responding to a small number of analytes), this is *nowhere near* the broad scope of the invention that is claimed.

First of all, the invention as claimed extends beyond providing a cell that comprises a promoter element that can respond to an analyte, since there is no requirement in claims 29-48 that requires the presence of a promoter element. The specification fails to teach any other manner in which an analyte can be detected. It is important to note that all of the references referred to in the Appendix concern the use of promoter elements to detect analytes. Thus, the references are insufficient to support Applicant's arguments that the full scope of the invention is described and enabled based on that issue alone.

Furthermore, even if the claims were limited to cells comprising promoter elements that responded to an analyte to produce a detectable signal, the full scope of the claims is neither described nor enabled. The specification and the state of the art at the time of filing only teach a few promoter elements capable of detecting a few select analytes, whereas there are literally millions of "analytes" that exist. Applicant even acknowledges that there are not elements "to detect every possible analyte in a universe of different analytes" in their response, which is the basis for the rejection. In essence, Applicant is acknowledging that the full scope of their claimed invention is not enabled.

In the previous Office Action, the Office provided several examples of analytes for which no mechanism of detection is known (see for example the top paragraph of page 4 of the Office Action mailed November 5, 2004). Applicant provides *no response* as to how to make the invention with regard to those analytes, or even a description thereof, supporting the notion that Applicant has neither described, nor can they make or use the full scope of the claimed invention. As such, the arguments are not persuasive to withdrawn the rejections under 35 USC § 112, first paragraph.

3. While it is true that a "patent need not teach, and preferably omits, what is well known in the art," the specification clearly fails to teach elements that *are not known in the art*. This is evident from the acknowledgement by Applicant that "cells do not exist to detect every possible analyte in a universe of different analytes" (see specifically page 14, lines 9 and 10 of Applicant's remarks). Thus, the previous statement about not disclosing "what is well known in the art" is irrelevant to the instant rejection, because the rejection is based upon what is not known in the art, as opposed to what is well-known but omitted (as argued by Applicant). The same argument

can be made with regard to Applicant's argument that they only need to describe "what is new or not conventional in the art." It is reiterated that the Office provided several specific examples of analytes that cannot be detected by means which are disclosed in the instant specification or in the state of the art at the time of filing (again, see for example the top paragraph of page 4 of the Office Action mailed November 5, 2004). Applicant has not addressed any of these issues, again suggesting that cells for detecting those analytes (as well as millions of others) were not described or enabled at the time the instant specification was filed.

4. The assertion that Applicant has disclosed a "representative number of species" to describe the genus of all manners in which to produce a detectable signal in response to any analyte does not appear to be correct. As set forth above, the instant specification only describes response elements that promote the expression of a protein in response to a particular compound (mercury), wherein that protein produces a detectable signal. This in no way describes a manner to produce a detectable signal in response to an analyte that does not involve the use of a promoter response element.

Furthermore, the single example of a mercury response element is not representative of *any* response element. Applicant provides an Appendix referring to a number of different promoter response elements capable of directing the expression of a detectable gene in response to a particular analyte. However, each of these promoter elements are structurally distinct because they each have distinct nucleic acid sequences required to respond to the corresponding analyte. For example, as set forth in the previous Office Action (see for example page 7, lines 5-15), the mer Ro/p element does not respond to other analytes such as benzene or toluene, and thus must not have a structure (i.e., nucleic acid sequence) that responds to those analytes.

Notably, Applicant does not traverse the accuracy of this statement in response to the previous Office Action. Since this is true, it is impossible for the mer Ro/p element to represent those other promoter response elements in a species-genus manner, because it does not retain a structure that describes those other structures.

Instead, the skilled artisan would be required to identify new promoter response elements for each and every analyte that is not present in the short list (relative to the millions of compounds which are contained within the definition of analytes, a list of 35 promoter elements is considered short). This represents a vast amount of undue and unpredictable trial and error experimentation from the skilled artisan, who must empirically identify new promoter elements for each and every analyte (if such promoters exist), there being no way to predict which promoter elements can detect a given analyte based upon the structure of the mercury promoter element.

5. It is first noted that the previous Office Action explicitly states why one would not expect to extrapolate the single example set forth in the instant specification across the full scope of the claims. Specifically, the previous Office Action states that the mer Ro/p element does not respond to other analytes such as benzene or toluene, and thus must not have a structure (i.e., nucleic acid sequence) that responds to those analytes (see for example page 7, lines 5-15). Therefore, there is no way that the skilled artisan could take the mer Ro/p element and predict the structure of an element that detects benzene, toluene, etc., or even one of the several analytes the Office indicates as having no known promoter element (such as carbon tetrachloride or telocidin). As such, Applicant's statement that the skilled artisan could extrapolate from the mer

Ro/p element to predictably create a promoter element that responds to any other analyte is not correct.

As a result, Applicant's arguments are not found convincing, and the Enablement and Written Description rejections are maintained.

NEW REJECTIONS

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 8, 10-12, 16, 18, 19, 23, 25, 27 and 29-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyngberg (as cited in the previous Office Action mailed October 21, 2003) in view of Banesmir (US 4,847,197; see entire document; henceforth Banesmir). **This is a new rejection that is not necessitated by amendment.**

In the Office Action mailed October 21, 2003 (see for example pages 8-10), it was established that Lyngberg taught the following:

Lyngberg teaches a single-use Hg(II) (i.e., divalent mercury) patch biosensor device/apparatus comprising bacteria (specifically *E. coli*) that express a luciferase gene that has been operably linked to a mercury-sensitive regulatory element (e.g., an operator), where the bacteria is immobilized/encapsulated in a latex polymer matrix (see for example the Abstract, page 668-669, the bridging paragraph). A diagram of the device/apparatus containing the biosensor is provided in Figure 2 (see for example page 670), where it is clearly shown that the immobilized bacteria are attached to a polyester support matrix. The small nature of the device/apparatus indicated in Figure 2 (the apparatus is only approximately 15mm in length) inherently confers the property that it can be carried by hand. The mercury-sensitive regulatory

element that is used is the mer Ro/p element (see for example Figure 1 on page 669). The particular bioluminescent reporter gene that is used is the *luxCDABE* gene cluster (see for example Figure 1 on page 669). These elements are incorporated into the bacteria on a plasmid, such as pRB28 (see for example Figure 1, page 669). This construct allows the identification of divalent mercury in a sample because the divalent mercury activates the expression and resulting activity of the bioluminescent lux gene product. The lux gene product can be detected using film (see for example page 668, right column first full paragraph), thus a camera or other film-containing device can serve as a portable detection device. Additionally, according to the specification, the lux gene emits visibly detectable light (see for example page 5, lines 18-19 of the instant specification), thus the human eye can also serve as a portable detection device. Lyngberg additionally teaches using the device to detect the presence of mercury in water samples (see for example page 668, left side, first full paragraph) as a less expensive alternative to chemical methods.

In short, Lyngberg teaches the use of encapsulated bioluminescent bacteria (i.e., comprising a Mer Ro/p element fused to a lux gene) for the identification of analytes in a sample. However, Lyngberg does not teach placing the bioluminescent bacteria on a filter strip impregnated with a nutrient solution.

Banesmir teaches the formulation of a "test strip" (see for example column 2, lines 20-44), wherein the test strip comprises the presence of bioluminescent bacteria on a strip of filter paper (see for example column 2, lines 20-25). Significantly, Banesmir teaches that the filter strip can be impregnated with nutrient medium and/or placed in a storage container (see for example column 2, lines 27-38). Banesmir teaches that using "test strip" comprising luminescent bacteria represents a quick and easy method that can be carried out even by unskilled persons to give reliable qualitative and quantitative results.

It would have been obvious to combine the Lyngberg and Banesmir references because both references utilize luminescent bacterial cells as detection agents, and since one bioluminescent bacteria can be placed on a filter paper for detection purposes, it would be obvious to place the other bacteria on a filter paper as well. The ordinary skilled artisan would

have been motivated to combine the teachings of Lyngberg and Banesmir because placing bioluminescent bacteria on a filter strip comprising a nutrient broth medium develops a quick and easy method of using the bacteria as a detection agent (as taught by Banesmir); thus, Lyngberg would obviously be motivated to put their bacteria on a filter strip to allow even the unskilled artisan to make use of their bioluminescent bacteria as an agent for detecting mercury. Absent evidence to the contrary, and considering that there is nothing substantially different between one type of bacteria over another as it relates to placing the bacteria on a filter strip, the ordinary skilled artisan would have had a reasonable expectation of success when placing the bioluminescent (taught by Lyngberg) onto filter paper (as taught by Banesmir) for the purpose of testing solutions.

Claims 1-3, 5, 8, 10-12, 16, 18, 19, 23, 25, 27 and 29-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyngberg and Banesmir in further view of Simpson (as recited in a previous Office Action mailed October 21, 2003). **This is a new rejection that is not necessitated by amendment.**

Lyngberg and Banesmir teach the elements set forth above in the rejection of claims 1-3, 5, 8, 10-12, 16, 18, 19, 23, 25, 27 and 29-48 under 35 USC § 103(a). However, Lyngberg and Banesmir do not specifically teach the use of *Pseudomonas fluorescens* as the bioluminescent bacteria.

Simpson teaches a bioluminescent bioreporter integrated circuit for the detection of heavy metals in samples such as water (see for example the Abstract). The bioreporter comprises a genetically modified microorganism such as a bacterial strain, where the bioreporter

is either integrated into the chromosome of the organism, or maintained on plasmids (see for example column 1, lines 25-35). In a specific embodiment of the invention, the bacterium used in the bioreporter is a *Pseudomonas fluorescens* strain (see for example column 3, lines 15-32), and a preferred bioreporter is the *Vibrio fischerii luxCDABE* gene product (see for example column 23, lines 20-23), which can be linked to a promoter that is responsive to an environmental factor (see for example column 23, line 65 to column 24 line 18). Importantly, Simpson references the ability to detect environmental factors such as Hg(II) by placing the promoter of interest in front of the promoterless *lux* genes from *Vibrio fischerii* (see for example column 1 line 63 to column 2, line 5).

It would have been obvious for the skilled artisan to combine the teachings of Lyngberg and Banesmir with the teachings of Simpson because both are related to achieving the same process: the detection of heavy metals (such as mercury) in water samples by using a bacteria comprising a bioluminescent reporter gene operably linked to a promoter element that is responsive to the heavy metal to be detected. The ordinary skilled artisan would have been motivated to combine the teachings because, as taught by Simpson, the use of *Pseudomonas fluorescens* to detect divalent mercury is a preferable embodiment. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when combining the teachings of Lyngberg and Banesmir with the teachings of Simpson.

Claims 1-3, 5, 8, 10-12, 16, 18, 19, 23, 25, 27, 29-48 and 9* are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyngberg, Simpson and Banesmir (as applied to the rejection of claims 1-3, 5, 8, 10-12, 16, 18, 19, 23, 25, 27, 29-48, above) in further view of King et al.

(IDS reference C10; see entire document; henceforth King). Note-* represents the claim rejected by the new combination of references. **This is a new rejection that is not necessitated by amendment.**

Lyngberg, Banesmir and Simpson teach the elements set forth above in the rejection of claims 1-3, 5, 8, 10-12, 16, 18, 19, 23, 25, 27 and 29-48 under 35 USC § 103(a). However, Lyngberg, Banesmir and Simpson do not specifically teach the use of *P. fluorescens* 5R.

King teaches the use of *P. fluorescens* 5R for the detection of analytes via the activation of a bioluminescent reporter gene (see for example page 779, Figure 1). Thus, King teaches that the specific strain *P. fluorescens* 5R can be used successfully for the bioluminescent detection of analytes.

It would be obvious to combine the teachings of Lyngberg, Banesmir and Simpson with the teachings of King because the host cell *P. fluorescens* 5R is a specific *P. fluorescens* strain, the genus of which has been suggested for use in the detection of divalent mercury by Simpson. The ordinary skilled artisan would have been motivated to use the *P. fluorescens* 5R host cell for the detection of divalent mercury because this strain has already been characterized for the production of a bioluminescent reporter gene in the presence of an analyte, and therefore offers the advantage of an expectation of success in producing a detectable signal. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when combining the teachings of Lyngberg, Banesmir and Simpson with the teachings of King.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Lambertson, Ph.D.
AU 1636

JAMES KETTER
PRIMARY EXAMINER